

FAX

Date 13 October 1999

Number of pages including cover sheet 2

TO:

JANE AXELRAD

301-594-6197

Phone

Fax

Phone

FROM: JORGE R. BARRIO

UCLA School of Medicine

Dept. Pharmacology

Div. Nuclear Medicine

La Conte Avenue

Los Angeles/CA

900956948

Phone

Fax

310 - 825 4517

Phone

CC:

REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please Comment

Dear Jane:

We thought that the section on profit-man-profit entities was not sufficiently clear in our letter of October 11. The enclosed letter (October 13) clarifies our views. We think that further discussions on this will be very helpful.

Regards

Jorge

98D-0266

C6



26741 Portola Parkway
Suite 1 E-520
Foothill Ranch, CA 92610

PHONE (714) 649-0427
FAX: (714) 649-3548
E-MAIL: icpmail@aol.com
WEB ADDRESS: www.icppet.org

PHYSICIAN
Ruth Deans, FRCR
ICP Medical Director

PHYSICIAN
Susan L. Wallace, Ph.D.
ICP Medical Director

PHYSICIAN
Vol Lowe, M.D.
St. Louis University School of Medicine

PHYSICIAN
Peter S. Conti, M.D., Ph.D.
USC School of Medicine and Pharmacy

Jorge R. Barrio, Ph.D.
ICP Medical Director

R. Edward Coleman, M.D.
Ohio University Medical Center

Sanjiv Ghandhi, M.D., Ph.D.
ICP Medical Director

Kathy Hunter, CNMT
University of Tennessee Medical Center

Michael F. Phelps, Ph.D.
UPenn School of Medicine

Martin Sandler, M.D.
Vanderbilt University

Paul Shewar, M.D.
University of Michigan Medical Center

Garner S. Young, D.O.
Madison Medical Center of Illinois

PHYSICIAN
Peter E. Volk, M.D.
Madison California PET Imaging Center

PHYSICIAN
Jennifer S. Keppler

October 13, 1999

Ms. Jane Axelrad, J.D.
Associate Director of Policy
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Axelrad:

As a point of clarification to our letter of the 11th of October 1999, we would like to stress two important points:

- (i) The intent of our first **general** comment was to delineate the various **alternatives** that we **felt** should be available for **manufacturing PET** drugs and to **clarify the boundaries** of FDA jurisdiction from **the** activities that would remain within the practice of pharmacy and medicine. We believe **that** FDA **regulatory** jurisdiction **over** a manufactured batch of a **radiopharmaceutical** (whether that is a manufactured **unit** dose, several unit doses, **or** multi **dose** vial) should **end with** the **QC** release of **the** final product. **Dispensing** and administration **to** a patient **always** takes place **under the regulations** governing the practice of pharmacy or medicine.
- (ii) Specifically, **the** issues regarding the delineation of **the** manufacturing process and **the** practice **of** pharmacy **and** medicine should not **have** any **connection with** a **definition** of **profit/non-profit entities**. **The** latter is a complex issue and, it is our understanding, **has been deferred** by the **FDA**. **WC** look **forward** to discussing this **definition** with the **FDA** in the very near future.

Sincerely,

Jorge R. Barrio, Ph.D.
Chairman, Radiopharmaceutical Committee

Jennifer Keppler
Executive Director, ICP

FAX

Date 10/11/99

Number of pages including cover sheet 6

TO:

Jane Ayelord

Phone

Fax

Phone

301-594-6197

CC:

FROM:

Jape N. Barris

UCLA School of Medicine

Dept. Pharmacology

Div. Nuclear Medicine

LA Conte Avenue

Los Angeles/CA

90095-6948

Phone

Fax

Phone

310-825 4517

REMARKS:



Urgent



For your review



Reply ASAP



Please Comment

Dear Jane,

Thank you for the opportunity
to review your C6MPs. Our community
are involved.

Regards

Jape



October 11, 1999

26741 Portola Parkway
Suite 1E-520
Foothill Ranch, CA 92610

PHONE: (714) 649-0627
FAX: (714) 649-3548
E-MAIL: icpmail@aol.com
WEB ADDRESS: www.icppet.org

Ms. Jane **Axelrad, J.D.**
Associate Director of Policy
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20847

Ruth Dunn Jones
SFFMC Boardmember, unexpired term

Susan L. Wallace, Ph.D.
 City Manager and Treasurer

Val Town, M.D.
St. Louis University School of Medicine

Daniel S. Gurevitz, M.D., Ph.D.
Judeo-Socratic School of Medicine and Pharmacology

Jorge N. Bunker, Pl. D.
1.7A, Cubana y Matanzas

R. Edward Coleman, M.D.
Duke University Medical Center

Samir Gambhir, M.D., Ph.D.
UTSA School of Medicine

Kathy Hunter, CMAA
University of Tennessee Medical Center

Mr. David E. Phelps, Ph D
 1810 S. 1st St. of Memphis

Martin Sandler, MD
Vice President / Chairman

Paul Shreve, M.D.
University of Southern California

Curtis S. Young, DO
 Medical Director, Center of Wellness

Peter F. Weik, M.D.,
Non-Fluorinated Polymers (NFP) Discussion Coordinator

Jennifer S. Knudsen

Dear Ms. **Axelrad**:

We appreciate the opportunity to have an open discussion with you and FDA staff about Current Good Manufacturing Practices (CGMPs) proposed by the FDA for PET radiopharmaceuticals. Outlined below are the PET Radiopharmaceutical Committee's comments on the preliminary draft of CGMPs proposed by the FDA in the public meeting of September 28, 1999.

General Comments:

1. **Compounding, practice of pharmacy and medicine**, Any **reference to nomenclature** or **activities** traditionally associated with the **practice** of pharmacy and medicine should be removed **and/or** clarified. We **have tried to** outline in our comments below how **this** can be done.

The **ability** of a **manufacturer** to produce **either** multi-dose **vials** or [not-patient specific] single **dose syringes** should be maintain⁴ **in** either case, these can be **transferred** to **either** a **pharmacy** for **patient-specific** dispensing or **to** a duly licensed physician for **use** in his **practice**.

In academic/non-commercial sites (not for profit), the same person/group that is manufacturing the drug product may also, under the order of a physician, draw and dispense a patient specific-dose. In a commercial environment (for profit), a site may sell/distribute a vial to a licensed pharmacy, who on the order of a physician may draw and dispense a patient-specific unit dose, as per the practice of pharmacy. Alternatively, a site may choose to manufacture [not-patient-specific] single-dose syringes or vials that would go to a licensed physician for use. We recommend inclusion of language for a clear delimitation of FDA jurisdiction.

2. **Validation requirements** for USP methods as well as methods that have been in use for the many years in the preparation of well-established PET drug products should be minimized in the guidance. The committee believes that if the FDA implements the suggested validation guidelines, a considerable amount of unnecessary additional work will be required of each PET facility in order to produce a final product of the same quality as is being produced currently. We also strongly believe that retrospective, repeated end product validation is an appropriate mechanism for validation of many of the methods used in preparation of well-established agents. To address areas of concern, the Committee will evaluate putting together a centralized DMF addressing the validation of analytical quality control methods for reference by the PET community. The committee would appreciate additional recommendations from FDA staff regarding other centralized efforts that may facilitate compliance with the proposed validation requirements by individual PET centers.
3. **Test Equipment Failures.** We respectfully request that the FDA give consideration to the development of guidelines that will permit the release of PET drugs in the absence of an analytical test result due to respective equipment breakdown. The release of final drug product could be based on (1) verification that monitoring of in-process controls has demonstrated that all parameters are within a normal range; and (2) historical data indicating that the parameter that could not be tested consistently is found within specifications. In the absence of such a guideline, PET centers will be required to duplicate, all analytical equipment at a considerable expense or delay diagnosis and treatment of patients being seen at a center.

We also suggest the following specific comments in the proposed draft CGMP document:

Section 212.1 Definitions

1. The following definition is added for "ACTIVE INGREDIENT".
Active ingredient: Any component that is intended to provide a direct effect in the diagnosis or evaluation of a disease or condition.
2. The definition for "compounded PET drug" should be removed. We realize that the term compounded PET drug is defined as such in FDAMA, however, its inclusion here without a concordant definition for manufactured PET drug is confusing. If the intent of its inclusion is to clarify that the regulations are applicable to both compounded PET drug Products as well as manufactured PET drug products, we recommend that this be addressed in Section 212.2. Also, the current definition of "compounded PET drug" implies that the CGMPs are applicable to PET drugs used for research, teaching, or quality control. If this definition remains, references to "research, teaching, and quality control" should be deleted.
3. The definition for theoretical yield needs to be removed and or clarified to include a range. This will also necessitate a change in the definition of "percentage of theoretical yield".

4. The definition for "receiving facility" should be modified as follows:
Receiving facility means any **hospital, imaging facility**, pharmacy, physician **office** or **other entity** that accepts a PET drug for subsequent dispensing for human use.

Section 212.40—Control of Components, Containers and Closures

1. **In section (c) (1) and (2), the requirement for performing specific identity tests should be waived if a certificate of analysis is available and the component is purchased from a reliable manufacturer. Reliability, as suggested in (2) can be defined in the guidance document, but could in part be based on having a track record use of the component without synthesis and/or component failures.**

Verification, without use of a specific identity test is **adequate, given a batch size of one** and final **drug product testing**. In traditional manufacturing practices, specific identity **testing is** grounded economically, because **of batch size** and the resultant cost in supplies and delays if the component **were to fail**. Such specific identity **tests** should not be required and, for the **single-employee** PET site, would represent an **unnecessary** burden.

Section 212.50—Production and Process Controls

1. **In (c) (1), it is not possible to prospectively define the strength of a PET drug, therefore should be modified to allow a range of acceptable strength.**
2. **In (c) (2), references to "dosage unit" are inappropriate. The requirement should be stated in terms of a "batch".**
3. **In (c) (5), reference to theoretical yield should be replaced or clarified to permit a range.**
4. **In (d), the 5th line should be modified to allow weights or measures of components to be used.**
5. **In (e), the reference to "dispensing" should be removed and replaced with the word packaging.**
6. **As discussed in (h), delete the requirement for maintaining a "reserve" sample for 30 days.**

Section 212.60—Laboratory Controls

1. **In section (d), prepared solutions should also be labeled with the date of expiration.**

2. In section (g) (2), during our discussion on September 28th, it was clarified that **the** reference to maintaining the weight and/or **measure** of the sample used in the test was **necessary only** as a part of **the written** "procedure" not in the record **itself** of each test. **Therefore, this sentence should be reworded as follows:**
(2) A description of each method **used** in the testing of the sample, which shall include a **record** of **all the** calculations that are to be used in connection with **each test, and** a specification of **the** approximate **weight or measure** of the sample to be **tested**.

Section 212.70—Finished Drug Product Controls and Acceptance Criteria

1. In section (b), sterility **tests** should be **started** within **24** hours of release, not immediately, in **the interest of** keeping radiation exposures as low as **reasonably** achievable.

Also in section (b), delete the statement "In addition, the doctor who wrote the prescription or the **PET** drug must **be** notified."

2. In Section (d) (2) – delete **"associated** laboratory data".

Section 212.80

1. In section (b), change to **"the date and time of calibration"**.

Section 212.90—Distribution

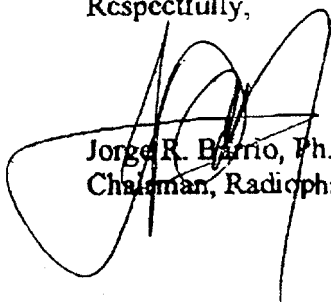
1. **Section (a)**, change "to ensure that only those products that are approved for **release are** used" to "to ensure only those **products** that are approved for release are distributed to **the** receiving **facility**."
2. Also in section (a), **delete** **"that** prescriptions **are** reviewed to **ensure that they are** properly filled".
3. **Section (b) (1)** should be modified to include the name of the receiving **facility** or physician.
4. **Section (b) (3)**, the words "patient's prescription, if applicable, or" should be **deleted**.

One of the most challenging things we face is trying to **convey** the intent of what is required into words that **will** be later interpreted properly. **The** PET community would **like** to develop a mechanism to **participate in the** 483 **review** process, to **facilitate implementation** of these regulations. **In this way**, the dialogue **that** has proven so **productive** over the past two years can **be extended through implementation**.

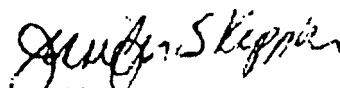
Thank **you again for the opportunity** to allow us to assist **you** and your **staff** in the **formulation** of **these** important regulations. **We** would like to **offer** our **continued** assistance in refining and developing **the** subsequent guidance for **their** interpretation. Since several members of your PET **team** will be in **Vancouver** on October **26th**, 1999 **for** the FDA-PET **workshop**, **we request** the opportunity to meet with you **and** your **staff** following **the** workshop to continue **these** discussions.

Please feel free to contact us if you have any questions or specific comments.

Respectfully,



Jorge R. Barrio, Ph.D.
Chairman, Radiopharmaceutical Committee



Jennifer Keppler
Executive Director, ICP